



FIGURE 2.39

Initial steps of the biosynthesis of purine nucleotides.

leads to the formation of inosine monophosphate (IMP), the precursor of ATP, GTP, dATP, and dGTP necessary for RNA and DNA formation. Only the steps most relevant to antitumor drug action are discussed here.

## 6.1 INHIBITORS OF PRPP AMIDOTRANSFERASE

The first irreversible step in *de novo* purine biosynthesis involves the nucleophilic displacement of the pyrophosphate group of PRPP by a molecule of ammonia, generated by hydrolysis of glutamine to glutamic acid. Both reactions are catalyzed by PRPP amidotransferase, whose main inhibitors are thio-purines (e.g., 6-mercaptopurine), acting through feedback mechanisms. These antitumor drugs have a complex mechanism of action, involving the inhibition of several enzymes related to purine biosynthesis and misincorporation into nucleic acids, and are discussed in Section 6.5.